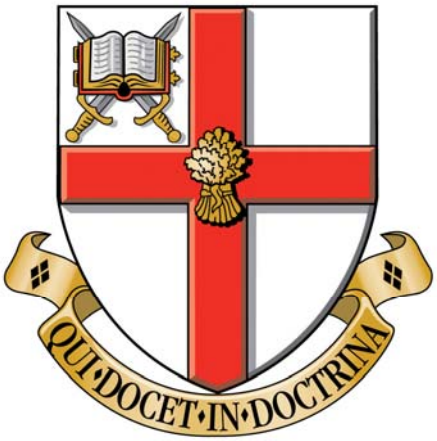

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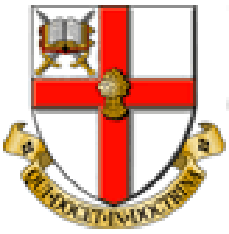

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“A Systematic review comparing the two cardiac procedures namely off-pump CABG and on-pump CABG in terms of the total patency rates”

Dissertation submitted in accordance with the guidelines of the University of Chester for the degree of Master of Science in Cardiovascular Rehabilitation.

September 2009

Dr. Fahad I. Merchant

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Glossary:

Cardio-Pulmonary Bypass (CPB) also known as the Heart Lung Machine (HLM) is a huge machine used to purify blood. It receives de-oxygenated blood and purifies it, thereby accomplishing the role of the human heart and lungs.

Coronary Artery Bypass Surgery (CABG) also known as **coronary artery bypass graft surgery** or the on-pump CABG is a surgical procedure performed to relieve angina and reduce the risk of death from coronary artery disease. Arteries or veins from elsewhere in the patient's body are grafted to the coronary arteries to bypass atherosclerotic narrowing's and improve the blood supply to the coronary circulation supplying the myocardium (heart muscle).

Grafting is a surgical procedure to transplant a healthy blood vessel which can be an artery or a vein to the diseased blood vessel.

Off pump Coronary Artery Bypass (OPCAB) is a type of coronary procedure whereby the cardio-pulmonary bypass is not used to bypass the function of the heart and lungs. Instead, the surgeon performs directly on the pounding heart. It has also been addressed as the beating heart surgery, off-pump surgery.

Patency means the state or quality of being open, expanded, or unblocked. In this study its is related to the blood vessels which should remain open or unblocked after an operation

List of Abbreviations

BHACAS - Beating Heart Against Cardioplegic Arrest Study

CABG – Coronary Artery Bypass Graft

CAD - Coronary Artery Disease

CCA - Conventional coronary angiography

CCAB = Conventional Coronary Artery Bypass Surgery

CI = confidence interval

COPD – Chronic Obstructive Pulmonary Disease

CPB – Cardio Pulmonary Bypass

HLM – Heart Lung Machine

LDL – Low Density Lipoprotein

MDCTA - Multidetector Computed Tomography Coronary Angiography

MI – Myocardial Infarction

OPCAB – Off Pump Coronary Artery Bypass

PTCA – Percutananeous Transluminal Coronary Angioplasty

RCT - Randomized Controlled Trials

SMART - The Surgical Management of Arterial Revascularization Therapies

Abstract

The objective of this study was to perform a systematic review analyzing the total patency rates in off-pump Coronary Artery Bypass Graft (CABG) and on-pump Coronary Artery Bypass Graft. For more than thirty years, surgical coronary revascularization has been accomplished with the use of cardiopulmonary bypass (CPB) in the vast majority of cases. However, off-pump coronary artery bypass grafting (OPCAB) has enjoyed a recent resurgence in interest and popularity, worldwide. The prime aim was to compare the two procedures and find out the total patency rates in each by there angiographic outcomes along with short and long term follow-up.

A total of seven Randomized control trials were included in the systematic review, and the articles were assessed and included if they fulfilled the criteria of Jadad scale and the guidelines of The Oxford Center for Evidence Based Medicine.

This review has yielded independent results in favour of both the surgical procedures. Each of the two surgical procedures has proved its efficacy when subjected to patients with different clinical profile. The papers and the method of selection of patients have been critically appraised in this study.

This study has reached a consensus declaring that both the procedures are equally effective when comparing the short and long term outcomes of the total patency rate. On the whole it depends on the surgeon, hospital, staff and other parameters to choose a procedure and the clinical status of the patient in order to approach a specific procedure.

INTRODUCTION

In this introduction there is a discussion on the overview of Coronary Heart Disease (CHD), and the process of Atherosclerosis and the factors which cause them. It is then followed by describing two procedures which are on-pump CABG and off-pump CABG; they have been described in detail in order to have a clear understanding about the procedure and for better understanding of these procedures diagrams have been displayed. Historical backgrounds are discussed after this in order to know how these procedures were invented and how they came into practice world wide.

Coronary heart disease refers to the failure of coronary circulation to supply adequate blood flow to cardiac muscle and surrounding tissue. It is already the most common form of disease affecting the heart and an important cause of premature death in Europe, the Baltic States, Russia, North and South America, Australia and New Zealand. It has been predicted that all regions of the world will be affected by 2020, (Boon, Colledge, Walker & Hunter, 2006).

CHD by itself is the most common cause of death in the U.K, around one in five men and one in six women die from the disease. CHD causes around 101,000 deaths in U.K each year, (British Heart Foundation, July 2007). Looking at the (National health Statistics for Britain, (2006); General Register Office ,(2006) Edinburgh, Scotland; General Register Office, (2006), Northern Ireland),

it shows that CHD is the most common cause of death in men, similarly women have 15% of deaths due to CHD.

The obstruction of the coronary arteries is due to atherosclerosis, which is gradual, often taking decades before the affected person is in danger of cardiovascular problems, (Abdou, Kerry & Lee, 2007). First, the inner lining of the artery is damaged. This causes white blood cells to gather at the site of the injury. This in turn provokes an inflammatory immune response that causes further damage to the artery wall. Over time, the endothelium is compromised and large, toxic Low Density Lipoprotein (LDL) cholesterol molecules can penetrate into the artery wall. The white blood cells and cholesterol combine to form lipid foam. In the early stages of atherosclerosis, these fatty streaks are present on the arterial wall as plaque deposits. Over time, the plaque may calcify, or form a hardened "shell." This reduces the supple artery's ability to contract and expand and narrows the artery, thus reducing the amount of blood that can flow through it. If the plaque deposit ruptures, a blood clot can form at the site of the rupture, or pieces of the plaque can travel through the arteries until they eventually cause a blockage. A heart attack and cardiac arrest may result, (Abdou, Kerry & Lee, 2007). Atherosclerosis can be caused by various factors such as smoking, increase in the LDL cholesterol, hypertension, diabetes mellitus and hyperhomocysteinemia.The figure 1 depicted below shows a schematic diagram of risk factors causing atherosclerosis.

Figure 1: Schematic design depicting the involvement of oxidized low density lipoprotein (oxLDL), injury of endothelial cells and proliferation of vascular smooth muscle cells (SMC) in the development of atherosclerotic plaque. MAP Mitogen-activated protein, (Singh, Mengi, Xu, Arneja & Dhalla, 2002)

Angiotensin II is the main mediator of the renin-angiotensin-aldosterone system, which maintains the physiological salt and water balance, blood pressure and vascular tone in the body. It is believed to be involved in atherosclerosis, (Arakawa & Urata, 2000) and endothelial dysfunction. It basically acts by releasing the reactive oxygen species which causes a series of cascade leading to the formation of atherosclerosis.

Untreated, CAD usually continues to worsen. Many CAD patients have symptoms such as chest pain (angina) and fatigue, which occur when the heart isn't receiving adequate oxygen. As many as 50 percent of patients, have no symptoms until a heart attack occurs, (Abdou, Kerry & Lee, 2007). Treatment generally aims to reduce cardiac workload, improve coronary artery blood flow,

and, over the long term, halt and reverse the atherosclerotic process. Coronary blood flow can be improved by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

Before going ahead a quick diagram to illustrate the coronary arteries and the anatomy of the vessels is displayed in the figure below

Figure 2: Basic anatomy of the coronary arteries of heart.

Source:
(http://www.nsh.nsw.gov.au/services/nscec/education/booklets/003683872-365.jpg)

Coronary Artery Bypass Graft (CABG)

Coronary artery bypass surgery (CABG), also known as coronary artery bypass graft surgery, is a surgical procedure performed to relieve angina and reduce the risk of death from coronary artery disease. Surgeons use segments of the patient's own veins and arteries to go around, or bypass atherosclerotic narrowing and improve the blood supply to the coronary circulation supplying the myocardium.

Figure 3: The figure above depicts diseased heart and the heart with bypassed blood vessel. Source: (http://www.columbiasurgery.org/pat/cardiac/cabg.html).

The most frequently used acronym for this type of surgery is CABG pronounced ‘cabbage’, (American Heart Association, 2006). There are two different methods of doing CABG: the traditional way, which is called the on-pump CABG, and the newer way, which is called the off-pump CABG. Opinion is

still divided on which is the better way. Most CABG is performed via midline sternotomy (middle cutting of the sternum bone).

On-pump CABG is a time-honored procedure that is performed while the heart is stopped. The blood supply must be provided to the rest of the body when the heart is stopped. Therefore, surgeons use the cardiopulmonary bypass machine (CPB) (also known as the heart-lung machine or the pump), an artificial circulation system that does the work of the heart and the lungs. Pipes are placed in the heart to drain the deoxygenated blood to the pump, where it is oxygenated and pumped back into the patient, (Shekar, 2006). Thus, the heart can be safely stopped with specialized cardiac medications that not only keep it stopped but also nourish it when it is still. The bypass grafts are then constructed. At the end of the procedure, the heart is restarted. When it resumes adequate function, the cardiopulmonary bypass machine is disconnected after the pipes are withdrawn from the heart. On-pump CABG today is a safe procedure that has a small risk of death and/or complications. The average risk of this procedure to a low-risk patient is 1% to 2 %,(Schachner, Zimmer, Nagele, Laufer & Bonatti, 2005). Even though there is still a conflict of studies which compare the on-pump and off-pump procedures to find out if there is a better technique and results over the other. Large trials are still going on to compare these procedures and to find efficiency in each of them in respect to the patient's clinical profile.

Figure 4: Typical heart lung machine used during CABG, **Source**:

(http://www.transonic.com/on_vs__off_pump.shtml)

The above figure 4 depicts a typical heart lung machine which is used in on-pump CABG. The pump plays the role of the heart and lung. Cardiopulmonary bypass consists of two main functional units, the pump and the oxygenator which removes the deoxygenated blood from a patient's body and replaces it with oxygenated blood through a series of hoses. The oxygenator is designed to transfer oxygen to infused blood and remove carbon dioxide from the venous blood. Further the complete procedure is explained in the section of Historical backgrounds.

Off Pump Coronary Artery Bypass Graft Surgery (OPCAB)

Off-pump CABG is considered the newer method of performing CABG. The complications of on-pump CABG, especially stroke and decrease in higher mental function, spurred the development of this technique. This procedure is performed with the heart beating and without the use of the heart-lung machine. Hence eliminating the placement of special pipes for the machine, use of artificial circulation, and excessive manipulation of the aorta, this technique introduces a new complexity of attaching grafts to the heart while it is constantly moving and filled with blood, a situation similar to “threading a needle on a rocking boat”. Special devices can mechanically stabilize the relevant part of the heart so that the suturing can be performed on a relatively immobile platform, (Detter, Deuse, Christ, Boehm, Reichenspurner & Reichart, 2002).

The figure 6 below depicts the instrument now widely used for OPCAB. It is known as an Octopus, it is a mechanical coronary stabilizer which attaches itself to the epicardium, and hence the area to be operated is silent while the rest of the heart is still beating. Therefore this procedure is also known as a beating heart surgery because the surgeons operate the diseased artery while the heart is still beating. This requires a great skill and therefore a learning curve is observed in this technique.

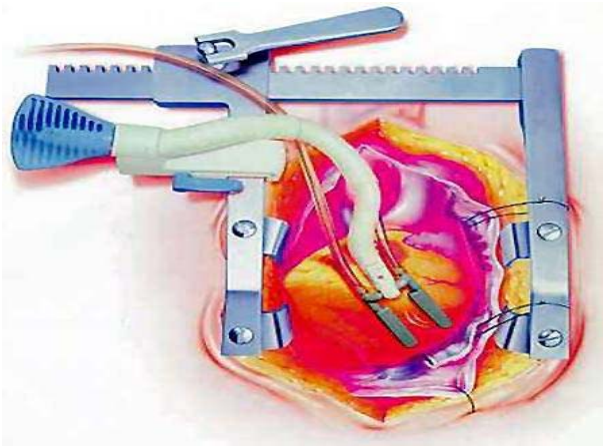

Figure 6: The Octopus (White colour instrument), **Source**: http://www.library.nhs.uk/theatres/page.aspx?pagename=ED13). From National Institute for Clinical Excellence

There have been concerns that poor grafting technique could result from constant motion that can jeopardize the quality of these grafts. However, surgeons who have adapted and perfected this technique have excellent results, (Puskas et al., 2004). In early to mid 1997, several North American surgeons became interested in using the Medtronic Octopus System (Medtronic, Inc, Minneapolis, MN). In 1998, Jansen and coworkers reported the design, experimental evaluation, and the first clinical use of this novel suction-based mechanical coronary artery stabilizing system. After Federal approval of the device, they began clinical application of this stabilizer, (Spooner, Hart & Pym, 1999). Early experience with the device was limited to vessels on the anterior surface of the heart, which were easily bypassed with excellent stabilization. Lateral and posterior vessels presented technical challenges because hemodynamic tolerance to the cardiac displacement necessary for exposure was poor. After experimental evaluation of the hemodynamic consequences of

vertical cardiac displacement, techniques were developed and shared and gradually more surfaces of the heart could be approached safely, (Grundeman et al., 1999). In early 2000, 18% to 20% of all coronary bypass operations were performed off-pump, (Mack, 2000); yet, there is wide variability between centers, and the whole field is subject to large swings based on new technology and new outcome studies.

Historical Backgrounds

CABG:

In 1935, Claude Beck of the Cleveland Clinic published his classic paper, “The development of a new blood supply to the heart by operation,” which described his technique of grafting a flap of the pectoralis muscle (Muscle of chest), over the exposed epicardium to create a new blood supply, (Beck, 1935). His work in myocardial revascularization spanned more than 30 years and captured the imagination of many surgeons. Arthur Vineberg in 1946 used the internal mammary artery to provide a new source of blood to the myocardium, (Vineberg, 1946). This technique became very popular; about 5,000 such operations were performed between 1950 and 1970.

Wilfred Bigelow and his team performed open-heart procedures in animals with the use of hypothermia in 1949, (Bigelow, Lindsay & Greenwood, 1950). This prompted more research on the applicability of hypothermia in human beings. In 1953, John Lewis performed the 1st successful closure of an atrial septal defect in a five-year-old girl, using the open-heart hypothermic technique that Bigelow's group had developed, (Lewis & Traufic, 1953). In the decade between the mid-fifties and the mid-sixties, surgical research was very much focused on various techniques of hypothermia and their possible clinical application.

Figure 7: Diagram shows the main coronary arteries and its branches

Source: (http://images.main.uab.edu/healthsys/ei_0028.gif)

On May 2, 1960, Robert Goetz performed a right internal thoracic artery-to-right coronary artery anastomosis using a tantalum ring in a 38-year-old man. Cardiac catheterization on postoperative day 14 showed a patent stented anastomosis which means that the coronary artery was open and no blockage could be seen near the anastomosis and the tantalum ring was intact without any blocks. The patient was anticoagulated with warfarin which is a drug and remained free of angina for a year. He died at Jacoby Hospital, Bronx, NY, on June 23, 1961, of a posterior wall myocardial infarction. Autopsy was not

performed, and the long-term patency of the anastomosis was not established, (Cushing, Magovern & Olearchyk, 1986; Olearchyk, 1988). Hence in 1964, Vasilii Kolessov, a Russian cardiac surgeon, performed the 1st internal mammary artery–coronary artery anastomosis, (Kolessov, 1967). Thus, Kolessov not only was the first to perform and the first to report successful suture CABG, but also the first to achieve long-term success after CABG, as well as the first to use with long-term success the internal thoracic artery, the graft of choice in modern coronary surgery.

Rene Favaloro and his colleagues from the Cleveland Clinic are fairly regarded to be the first in America to perform and report successful CABG. It is absolutely true that CABG was revolutionized by the Cleveland Clinic team. In 1968, they performed 171 operations, (Favaloro, Effler, Cheanvechai, Quint & Sones, 1971). It was the Cleveland Clinic team that convinced the world, and their contributions cannot be overestimated. After that Dudley Johnson extended the bypass procedure to include the left coronary arterial systems, (Johnson, Flemma, Lepley & Ellison, 1969). In 1968, Charles Bailey and Teruo Hirose and George Green used the internal mammary artery instead of the saphenous vein for bypass grafting. Today, coronary artery bypass grafting has become one of the most common operations and is performed all over the world.

OPCAB:

Contrary to the suggestion of Ascione and coauthors that “operation on a beating heart is a relatively new surgical procedure,” (Ascione et al., 1999). OPCAB surgery is not a new technique. In the 1950s, before CPB came into widespread use, Murray and Longmire performed a coronary endarterectomy with saphenous vein or internal mammary artery grafts, (Westaby & Bennetti, 1996). Endarterectomy means surgically removal of the plaque from the artery, and then they used saphenous vein which is the leg vein from the patients own body or they took an artery supplying the mammary gland as a graft for the bypass, (Westaby & Bennetti, 1996). Myocardial revascularization by anastomosing the internal mammary artery to the coronary artery was advocated by Demikhov in 1962, who undertook a canine study of this technique in 1952; four of his dogs survived for more than two years with patent grafts. In a similar time frame, Murray independently achieved similar results, (Westaby & Bennetti, 1996). In 1962, Sabiston used a saphenous vein graft to bypass the right coronary artery, and in 1964, Garrett bypassed the left anterior descending artery, (Westaby, 1997). That same year, Kolessov anastomosed left internal mammary artery (LIMA) to a marginal branch of the circumflex artery, (Spencer, Galloway & Colvin, 1995). All of these procedures were done off-pump on a beating heart. This shows that they were performing OPCAB even before CABG and the previous surgeons did develop the skills of performing the surgery on a beating heart.

After 1968, CABG with CPB was widely adopted, but OPCAB continued to be performed by some surgeons, (Favoloro et al., 1970; Ankeney, 1975). Hence, OPCAB was originally the only possible approach and, after the advent of modern CPB techniques, was largely viewed as outmode, (Cooley, 2000). However, with the introduction of minimally invasive coronary surgery and mechanical methods of target-artery stabilization, interest in OPCAB has been renewed. Now it is widely performed around the world with many surgeons following the trend to adopt it back again.

Cardio-Pulmonary Bypass (CPB)

The CPB oxygenates blood and circulates it throughout the body. The first step in initiating the CPB is to prime the tubing of the machine with a balanced electrolyte solution. The patient's blood is then brought to the pump either through one cannula being placed in the right atrial appendage or by two cannulas one being placed in the inferior vena cava which carries deoxygenated blood to the heart and the other in the superior vena cava which carries oxygenated blood to the heart. In addition, another cannula is placed in the ascending aorta to return oxygenated blood back to the patient's systemic circulation. For better understanding of the anatomy of heart, the diagram is depicted below in figure 8. Patients are also given an anticoagulant (blood thinner) called Heparin, which helps to prevent massive extravascular coagulation (clotting of the blood while out of the body in the CPB) while the blood is circulating through the mechanical parts of the bypass system. Once the

connection is established, blood is pumped through a circuit by a series of roller-type pumps. Venous blood from the patient flows through a venous cannula to a cardiotomy reservoir and then to the oxygenator where exchange of oxygen and carbon dioxide occurs. Blood goes through the heat exchanger in the bypass machine, it is cooled initially and then later it is rewarmed. During the CABG surgery, the core body temperature is decreased to 28 to 32 degrees Celsius (82.4 to 89.6 degrees Fahrenheit).

Figure 8: A diagram showing basic anatomy of heart.

Source: (http://www.cheresources.com/cardiopul.shtml)

This cold temperature of the body, which decreases metabolism, helps to protect major organ systems from ischemic injury (lack of blood flow to an organ of the body that results in damage to that organ). Oxygenated blood is then

filtered and returned to the patient's ascending aorta by way of the arterial cannula. Once extracorpeal (outside the body) circulation and hypothermia are acheived, the aorta is cross-clamped which means that no blood supply can pass through it which is just above the coronary arteries. Blood Cardioplegic solution is then infused in the aortic root. Once the aorta is cross-clamped, no blood goes through the coronary arteries, so the myocardium is ischaemic. The heart is then relaxed, the combination of asystole and hypothermia protect the heart against myocardial ischemia. Iced normal saline is also placed directly on the heart to make sure all parts of the heart are hypothermic. The cold technique is used at the end of the CABG surgery, the blood is rewarmed to 37 degrees Celsius (98.6 degrees Fahrenheit) using the heat exchanger in the bypass machine. The aortic cross clamp is removed so that the blood perfuses coronary arteries, which warms the myocardium. After the heart rhythm is maintained, and then the cardiopulmonary bypass is reduced to partial bypass. If the patient tolerates this then the heart assumes total responsibility for cardiac stability and the CPB is discontinued. The cannulas placed in the heart are removed and the patient's chest is closed. This is the actual procedure how a CPB works.

The death of a young patient in 1931 first stirred Dr. Gibbon's imagination about developing an artificial device for bypassing the heart and lungs, allowing for more effective heart surgery techniques. He was dissuaded by all with whom he broached the subject, but he continued his experiments and invention independently. In 1935 he successfully used a prototype heart-lung bypass machine to keep a cat alive for twenty six minutes. He began a new series of

experiments with dogs in the 1950s, using IBM-built machines. The new device used a refined method of cascading the blood down a thin sheet of film for oxygenation, rather than the original whirling technique that could potentially damage blood corpuscles. Using the new method, twelve dogs were kept alive for more than an hour during heart operations. The next step involved using the machine on humans, hence in 1953 during the repair of an atrial septal defect and was a major advance in open-heart surgery, (Gibbon, 1978).

In “Milestones in Chest Surgery,” Eloesser wrote, “Gibbon's idea and its elaboration take their place among the boldest and the most successful feats of man's mind.”, (Eloesser, 1970). Hence after this invention many other improvements were done in order to improvise the technique of CPB. The CPB has not changed much in the past 30 years. It is a large machine that takes up a lot of room in an operating room. Engineers are working on designing a smaller unit that will not take up as much room.

Rationale and Aim of the Review:

On-pump CABG and Off-pump CABG are the two most important type of cardiac surgeries performed globally now. Hence comparing these two procedures and to find out the efficacy of each procedure in the form of Patency rates will form the topic of discussion. The purpose of this review is to find out the efficacy of the two procedures and there benefits to the patients in a short and long term perspective. The graft patency is compared and interpreted in order to find out if there is any significant difference when the above two procedures are performed on selected patients. Also the patency rates are then compared to see if there is any significant difference in the revascularization after given period of time.

This will be achieved through systematic review of relevant studies which comply with a particular selection and exclusion criteria. The key feature of this review will be to analyze each study using the Jadad, 3-item quality assessment scale for control of bias, (Jadad et al., 1996) and Oxford Center for Evidence Based Medicine, (Phillips, Ball, Sackett, Badenoch, Straus, Haynes & Dawes, 1998) and updated by, (Howick, 2009).

The findings of the existing studies of comparing On-pump CABG and Off-pump CABG have been analyzed to determine if they provide the information regarding the questions posed below.

- Does On-pump CABG improve the patency rates compared to Off-pump CABG in low to medium risk patients?

- Does Off-pump CABG improve the patency rates compared to On-pump CABG in low to medium risk patients?
- Does Off-pump CABG have an upper hand over On-pump CABG when compared with the patency rates and vice-versa?
- Does a Surgical skill matter when performing Off-pump CABG?
- Is there any significant difference in the patency rate in a short and long term prospective when both procedures are compared?

Study Design:

The present study was done using databases allowing free access selecting the most authentic and relevant study material. The University account was also used in searching the database.

Databases Used:

a) PubMed

b) Cochrane Database

c) Medscape

d) Google Scholar

e) Science direct

Criteria used for selection of an article:

1) Randomized control trials that were double or single blinded the patients and the staffs were used. In a single-blind trial, the researcher knows the detail of the treatment but the patient does not, while in a double-blind trial, one researcher allocates a series of numbers to 'new treatment' or 'old treatment'. The second researcher is told the numbers, but not what they have been allocated to. The second researcher does not know which treatment is being administered, and so cannot possibly tell the patient, directly or otherwise.
2) Prospective Randomized control studies were included which means that the patient was followed for a longer duration of time.
3) The studies carried out in past 8 years were given more importance.
4) Only full text articles were included in the study.

5) Only English language articles were included.
6) Only trials done on Humans were included.
7) Secondary data included in the analysis were excluded.
8) The articles comparing OPCAB and CABG with CPB were included, rather than those describing only one procedure.
9) Papers comparing graft patency and revascularization in both procedures were included. Other variables like cost effectiveness, mortality, morbidity etc were also included in the study. But only graft patency was compared.
10) Total graft patency was given more importance in this study, rather comparing arterial and venous graft each.
11) Articles which were not available online were accessed by emailing the authors and requesting them to provide their articles.

Articles were hand searched in addition to other databases, Journals which were directly accessed as a part to achieve the article are:

1) American Journal of Cardiology
2) American Heart Journal
3) American College of Cardiology
4) Annals of Thoracic Surgery
5) British Medical Journal
6) Circulation
7) Journal of Thoracic and Cardiovascular Surgery
8) Journal of American Medical Association

9) Lancet
10) New England Journal of Medicine

These journals were used because the topic was on comparing two cardiac procedures; hence the above journals provided recent and authentic material for the review and provided the recent papers with some of them giving free access. The journal who dint had free access, the authors were emailed and requested to give a copy of the paper.

Study Selection:

Randomized control trial was only taken in to consideration for the study. The papers were reviewed according to Jadad five point scales, (Jadad et al., 1996) (Appendix 1) and Center of Evidence based Medicine (Appendix 2)

The Jadad five point scale was utilized as an initial screening tool for minimizing the likelihood of publication selection bias. Articles were included in the study if they scored 3 or more on a five point scale. Any article scoring below three was excluded from the study

The Centre for Evidence based Medicine has designed criteria for reviewing a paper, hence only papers that grade I were taken into the study and rest were excluded.

Key Words:

Key words used to search the journal paper include:

1) OPCAB AND CABG
2) Off-pump AND On-pump CABG
3) OPCAB AND Graft Patency
4) CABG AND Graft Patency
5) Bypass surgery AND Patency
6) OPCAB AND CABG AND Graft patency
7) Off-pump AND On-pump CABG AND Graft Patency

Results: After searching through these criteria, seven papers were collected and study was performed to find the overall graft patency when compared with OPCAB and CABG with CPB. The articles which were selected for the reviewed were then accessed through electronic full text facilities. The diagram below depicts the study design for better understanding.

STUDY DESIGN

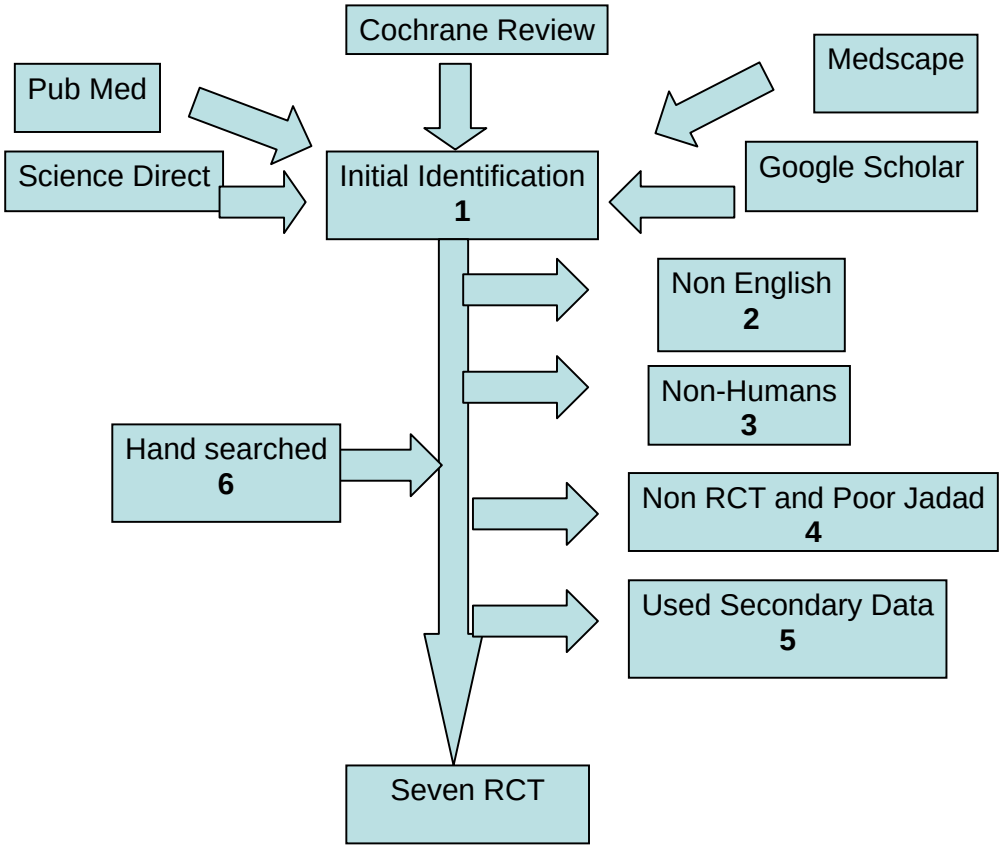

Fig 1) Flow chart illustrating how the articles were selected in the systematic review

RCT= Randomized Control Trials

AIM: Comparing the patency rates in on-pump and off-pump CABG

Introduction

The success of coronary artery bypass grafting (CABG) is dependent on the long-term patency of the arterial and venous grafts, (Lytle et al., 1985). Off-pump coronary artery bypass graft surgery (OPCAB) has been performed for many years and its use is increasing frequently, but it remains an open question whether OPCAB provides similar patency to conventional coronary artery bypass graft (CCABG) surgery with cardiopulmonary bypass (CPB). This is one of the most hotly debated and polarizing issues to date in cardiac surgery, (Sellke et al., 2005; Hannan et al., 2007 ; Karolak , Hirsch , Buth & Legare, 2007 ; Raja & Drefus, 2004).

Revascularization is a surgical procedure in which compromised or stenosed (narrowed) blood vessels are bypassed to treat ischemia. Hence in CABG the stenosed artery is bypassed by a graft (arterial or venous), in order to restore adequate amount of blood without any restriction of the flow of blood. More commonly used grafts nowadays are the right internal mammary artery, left internal mammary artery and great saphenous vein. Also synthetic grafts are being developed for better performance and reduction in graft rejection.

Carrel in I908 performed the first successful arterial homograft on a dog; hence in 1912 he was awarded the Nobel Prize for his work on the transplantation of blood vessels. A year later Lexer in 1913 reported that he had

resected three aneurysms of peripheral arteries and restored continuity in each case with an autogenous vein graft. But in 1949 Gross, Bill and Pierce published their adaptation of Carell's pioneer work to the treatment of coarctation of aorta (narrowing of aorta) and following this there was an interest in subjects to perform graft transplant.

To know about the patency of a graft and how much the graft is patent after 3, 6 or 12 months after surgery, a new instrument known as 64-slice multidetector spiral computed tomography (MSCT) is used. This instrument provides high diagnostic accuracy, sensitivity and specificity for the assessment of graft patency and native coronary arteries for the presence of stenosis, (Liu et al., 2008; Meyer et al., 2007). Hence by this instrument the patency rate can be found out and an outcome can be diagnosed. But previously the patency of a graft was diagnosed using different techniques. The coronary angiography was the method of choice few years back, (Khan et al., 2004; Puskas et al., 2004; Kobayashi et al., 2005 ; Lingaas et al., 2006) . Each graft was viewed in at least two orthogonal planes and scored on the worst appearance of the proximal anastomosis (if any), body of the conduit and distal anastomosis, generating a Fitzgibbon score, (Fitzgibbon et al., 1986) , by which comparisons were made between groups. A score of: 0- No flow or no perfusion

1- Slow penetration without perfusion

2- Partial flow or partial perfusion (>1 but <3)

3- Complete and brisk flow or complete perfusion, (Puskas, Vinten-Johansen, Muraki & Guton, 2001).

Therefore in these way a value for patency can be determined either postoperative or after 3, 6 or 12 months accordingly by the surgeon. These years the technology is advancing day by day. But still many surgeons still prefer the gold standard Conventional coronary angiography (CCA). The limitations of this procedure include a small but definable risk, the need for multiple staff members, and the cost related to the procedure itself and subsequent observational period. Because of this, alternative non-invasive methods like MSCT have been investigated for imaging of venous and arterial graft patency, (Gao et al., 2009). Hence MSCT is safe accurate and an effective way to find out the patency of the graft but still enough evidence still required to prove and replace the CCA and implication of a non invasive method.

Brief review of two papers not included in the study:

There is high-quality evidence that off-pump coronary artery bypass (OPCAB) grafting reduces the risk of postoperative morbidity and intensive care unit and hospital stays, (Cheng, Bainbridge, Martin & Novick, 2005 ; Wijeysundera, 2005), and uses fewer resources (Puskas et al., 2004; Nathoe et al., 2003 ; Ascione et al., 1999) than conventional surgery with cardiopulmonary bypass (CPB). However, only a minority of coronary artery bypass grafting (CABG) operations worldwide, about 15% to 20%, are carried out with the OPCAB technique , (Koegh & Kinsman, 2003 ; Cleveland et al., 2001).

The question arises why there is a debate between OPCAB and CABG with CPB. Both the techniques are well established but eventually the surgeons are the ones who decide which technique is appropriate for their patients in different circumstances. Therefore we are going to discuss the Revascularization and the Patency when compared with off-pump and on-pump CABG, and try to evaluate the success rate and the clinical outcomes of it in short, medium and long term follow-up. Therefore we go in the early 2000's and see the result of the trials which were done regarding the revascularization and patency when compared with on-pump vs off-pump.

1) In 2001 Martin Czerny and his colleagues did a randomized trial on the complete revascularization in coronary artery bypass grafting with and without cardiopulmonary bypass. Eighty selected low-risk patients were enrolled. In preoperative study with coronary angiography, the decision was made whether

complete revascularization without CPB could be performed. The patients were randomly assigned to receive CABG either with (n = 40) or without CPB (n = 40). Randomization criteria were age, sex, and left ventricular ejection fraction. Completeness of revascularization as well as short- and mid-term clinical outcome in a (13.4+- 6.5) month follow-up period was monitored. Revascularization was considered incomplete when a territory was judged surgically non-reconstructable or when a suitable vessel was discarded for technical reasons. In-hospital death, myocardial infarction, and stroke were defined as major adverse outcome. Minor adverse outcome was defined as wound infections and postoperative atrial fibrillation. In the group without CPB, 26 of 40 patients underwent revascularization (65%) of all target vessels, as intended preoperatively. Of the remaining fourteen patients, in five patients (12.5%) the intention of complete revascularization without CPB could not be accomplished because the vessel was judged surgically non-reconstructable due to a small luminal diameter. Nine patients (22.5%) were switched to CABG with CPB. The reasons for switch to CPB were deeply intramyocardial course of target vessels (n = 5, 12.5%) and hemodynamic intolerability during the exposure of the posterior wall (n = 4, 10%). While in the group of patients operated with CPB 34 out of 40 patients (85%) received complete revascularization of all target vessels as intended preoperatively. In six patients (15%) intra operative decision was made that the target vessels were not suitable for anastomosis due to a small luminal diameter. The results of this outcome was displayed in the form of a pie diagram below

Figure 1: Achievement of revascularization (Left, with CPB; right, without CPB), (Czerny et al., 2001).

(White shade indicates incomplete revascularization; Black shade indicates complete revascularization)

Conclusion: - CABG without the use of CPB is effective to achieve complete revascularization in the majority of selected low-risk patients. Nevertheless, the rate of incomplete revascularization in these patients undergoing CABG without CPB is higher. The rate of incomplete revascularization due to a small luminal diameter of target vessels is comparable in patients undergoing CABG either with

or without CPB. Hence while taking OPCAB as a procedure of choice it does give initial good results as compared to on-pump CABG but the only limitation is the long term revascularization and patency of the graft. In this study some patient's intra operatively was converted from OPCAB to CPB due to clinical reasons hence there is a definite limitation to the above study. Therefore this totally affects the clinical outcome of the study.

CABG without CPB has gained increasing acceptance for selected patients with single-vessel disease. Introduction of stabilizers made complete revascularization feasible even in multivessel disease, (Cartier et al., 2000). Complete revascularization in multivessel disease without CPB can be performed with low morbidity and mortality and excellent early angiographic results even in high-risk patients, (Cartier & Blair, 1999). These studies were done in the early 2000, but as new trials were performed the scenario changed accordingly. Still debate goes on when these two procedures are compared.

2) A study done by Khan and colleagues in 2004 was on a prospective, randomized, controlled study to compare graft-patency rates and clinical outcomes in off-pump surgery with conventional, "on-pump" surgery. They randomly assigned 50 patients to undergo on-pump coronary-artery bypass grafting and 54 to undergo off-pump surgery. Surgical and anesthetic techniques were standardized for both groups. Clinical outcomes and troponin T levels were measured. Three months later, the patients underwent coronary angiography, including quantitative analysis. Follow-up angiographic data were available for 82

patients (39 patients in the on-pump group and 43 in the off-pump group). The remainders were not willing to undergo repeated angiography. There were no systematic clinical differences between those who underwent repeated angiography and those who did not.

The overall patency rate for grafts performed on pump was significantly higher than the patency rate for those performed off pump (98 percent vs. 88 percent, P=0.002). This difference was observed in the territory of the right coronary artery (P=0.01) and the territory of the left anterior descending artery (P=0.07). Significantly more radial-artery grafts were used in the off-pump group, with a lower patency rate in this group than in the on-pump group (76 percent vs. 100 percent, P=0.01). Hence they found that the patency was better in the on-pump group than in the off- pump group, but the reason behind it also displays a different view about it.

The author considered possible reasons for the reduced patency rate in the off-pump group. The anticoagulation regimen differed in off-pump group, with only half-dose heparinization during the formation of the anastomoses. This practice is widely accepted, (Nathoe et al., 2003) and there have been no reports to suggest that it increases the risk of graft occlusion. All patients in both groups received the same regimen of antiplatelet therapy. The two surgeons performed similar numbers of on-pump and off-pump procedures for the study. In the two years preceding the study, the surgeons performed 13 percent of their coronary work off pump. Off-pump surgery is technically more demanding than on-pump

surgery because the operative field is less stable and less visible. The learning curve for this procedure is probably substantial and may be longer than they anticipated. Hence when interpreting the results some things should be taken in consideration, they used an unselected population of patients, many of whom had diseased target vessels. A more selective approach to the target vessel might yield better results for off-pump surgery. Hence we conclude that off-pump is as safe as on-pump CABG, but the graft patency rate is lower than on-pump in 3 months, so the concern is about long term patency rate and its outcomes.

Discussion: When we look at the two papers which are described above, it compares both the procedures in there own perspective. The outcomes are compared for a very short term, when longer outcomes need to be evaluated in order to find and interpret accurate results. Both the papers show that there is significant difference in the patency when compared with both the procedures.

But if we review both the papers closely, their scores are very low on a JADAD scale, (Jadad et al., 1996).Hence the studies are good but the protocol of an effective study is missing.

In the past few years there has been a change in the techniques and the surgeons are practicing the procedures more efficiently in order to find out the best result for the patient. Both procedures are effective in their own ways but to crack the code and to produce efficient results we will scrutinize more papers ahead in order to find the pros and cons along with efficiency of each procedure and their outcomes.

Table 1: Trial Characteristics

Author's name and year	No of patients enrolled Total (Off/On)	No of patients undergoing Angiography Total (Off/On)	Conversion to Conventional surgery, n (%)	Average Angiographic follow-up time	Patient Features and Exclusion criteria	Jadad Score	Level of Evidence
Nathoe et al., (2003)	281 (142/139)	70 (28/ 42)	10 (7)	12 months	Elective CABG, patient were excluded if poor LV function, MI < 6weeks, emergency major operation, Q wave MI.	3	Level 1 b
Lingaas et al., (2004)	120 (60/60)	115 (NR)	7 (12)	3 months	Elective CABG, patient were excluded if EF<30%, creatinine > 200mmol/L	3	Level 1 b
Lingaas et al., (2006)	120 (60/60)	109 (NR)	7 (12)	12 months	Elective CABG, patient were excluded if EF<30%, creatinine > 200mmol/L	3	Level 1 b
Puskas et al., (2004) (SMART)	200 (100/100)	153(76/77)	1 (1)	12 months	Elective primary CABG. IABP & cardiogenic shock patients excluded	4	Level 1 b

Table 1 continued

Author's name and year	No of patients enrolled Total (Off/On)	No of patients undergoing Angiography Total (Off/On)	Conversion to Conventional surgery, n (%)	Average Angiographic follow-up time	Patient Features and Exclusion criteria	Jadad Score	Level of Evidence
Kobayashi et al.,(2005)	167 (81/86)	167 (81/86)	0 (0)	< 21 days	Elective primary CABG. Age > 70yrs, indication for additional surgical procedure, H/o stroke, severe aortic calcification shown on Ct scan, carotid artery stenosis>75%, acute QWMI, emergency operation, LVEF< 30%, Sr creatinine >2 mg/dl, COPD, pulmonary HTN with pulmonary artery pressure >25mmhg.	3	Level 1b

Table 1 continued

Author's name and year	No of patients enrolled Total (Off/On)	No of patients undergoing Angiography Total (Off/On)	Conversion to Conventional surgery, n (%)	Average Angiographic follow-up time	Patient Features and Exclusion criteria	Jadad Score	Level of Evidence
Al-Ruzzeh et al., (2006)	168 (84/84)	151 (75/76)	0 (0)	3 months	Elective primary CABG. Left ventricular dysfunction with EF<30%, Renal failure with Sr creatinine .180 micro mol, emergency operation ,patient not ready for angiography after surgery, single vessel disease	3	Level 1b
Angelini et al., (2009) (BHACAS I & II)	401 (200/201)	199 (98/101)	0 (0)	7 years	Elective primary CABG. EF<30%, recent MI within 1 month, H/o supraventricular arrhythmia, previous CABG, renal or respiratory	4	Level 1a

					impairment, previous stroke, patient with coronary disease in the branches of the circumflex artery distal to the first obtuse marginal branch were excluded.		

CABG= coronary artery bypass graft, LVEF= Left ventricular ejection fraction, QWMI= Q wave myocardial infarction, COPD= Chronic obstructive pulmonary disease, MI= Myocardial infarction, SMART= The Surgical Management of Arterial Revascularization Therapies, BHACAS= Beating Heart Against Cardioplegic Arrest Study, EF= Ejection fraction, NR=Not Reported.

Table 2: Results Summary

Author & Year	% Undergoing CAG	No of Patent Arterial Grafts (%)		No of Patent Venous Grafts (%)		Total Graft Patency (%)		Result P value	Risk difference at (95% CI)
		Off	On	Off	On	Off	On		
Nathoe et al., (2003)	64 %	NR	NR	NR	NR	63/69 (91%)	83/89 (93%)	NS	2.0 (- 6.5 to 10.4)
Lingaas et al., (2004)	96%	52/54 (96%)	58/59 (98%)	72/86 (84%)	95/104 (91%)	124/140 (89%)	153/163 (94%)	NS	5.0 (-2.6 to 12.6)
Lingaas et al., (2006)	91%	48/51 (94%)	54/56 (96%)	67/84 (80%)	84/97 (87%)	115/135 (85%)	138/153 (90%)	NS	5.0 (-2.6 to 12.6)
Puskas et al., (2004) (SMART)	81%	95/101 (94%)	102/104 (98%)	140/150 (93%)	147/156 (94%)	235/251 (93.6%)	249/260 (95.8%)	0.27 NS	2.1 (- 1.7 to 6.0)
Kobayashi et al., (2005)	100%	245/263 (94%)	285/296 (97%)	16/17 (94%)	9/9 (100%)	261/280 (94%)	294/305 (96%)	0.093 NS	NR

Table 2 continued

Author & Year	% Undergoing CAG	No of Patent Arterial Grafts (%)		No of Patent Venous Grafts (%)		Total Graft Patency (%)		Result P value	Risk difference at (95% CI)
		Off	On	Off	On	Off	On		
Al-Ruzzeh et al., (2006)	90%	111/113 (98%)	111/114 (97%)	50/61 (82%)	60/68 (88%)	161/174 (93%)	171/182 (94%)	NS	1.4 (- 3.8 to 6.6)
Angelini et al., (2009) (BHACAS I & II)	57%	108/116 (93%)	113/126 (90%)	103/121 (85%)	115/129 (89%)	211/237 (89%)	228/255 (89.4%)	> 0.99 NS	1 (0.55 to 1.81)

NS= Not significant, NR= Not recorded, CAG= Coronary artery angiography.

Review of the Key papers:

Nathoe et al., (2003)

A Comparison of on-Pump and off-Pump Coronary Bypass Surgery in Low-Risk Patients.

Aim: The aim of this study is to compare the performance of coronary bypass surgery without cardiopulmonary bypass ("off pump") in reducing the perioperative morbidity and costs, but it is uncertain whether the outcome in term of patency is similar to that involving the use of cardiopulmonary bypass ("on pump").

Methods: In brief, after patients had given written informed consent, they were randomly assigned to off-pump or on-pump CABG. Patients were eligible if referred for first-time isolated coronary bypass surgery and an off-pump procedure was deemed technically feasible. Patients were excluded in case of emergency or concomitant major surgery, Q-wave myocardial infarction in the previous six weeks, or poor left ventricular function or if they were unlikely to complete one year of follow-up or unable to give informed consent. There were no restrictions as to age. The study was approved by the ethics committees of the participating centers.

Between March 1998 and August 2000, 281 patients were enrolled in three hospitals in the Netherlands, of whom 265 underwent treatment according to randomization. In ten patients randomized to off-pump surgery, CPB was used during the procedure. One other patient randomized to off-pump surgery underwent coronary angioplasty because of infection. In five patients assigned to on-pump CABG, an off-pump procedure was performed.

Results: 40 of the 110 preselected patients (36.4 percent) declined to undergo follow-up angiography because they had no symptoms. Angiography was performed in 42 patients (89 grafts) in the on-pump group and 28 patients (69 grafts) in the off-pump group. Graft patency in a randomized subgroup of patients was 93 percent after on-pump surgery and 91 percent after off-pump surgery. The P value was not significant with Risk difference at 95% Confidence Interval 2.0 (– 6.5 to 10.4).

Author's Conclusion: In low-risk patients, there was no difference in Graft patency at one year between those who underwent on-pump bypass surgery and those who underwent off-pump surgery. There was also comparison of the cost effectiveness and interpreted that off-pump was more cost effective than on-pump.

Reviewer's opinion & Limitations:

The focus of the study was on a relatively low-risk population of patients. The majority of the patients had single or double-vessel disease with preserved

ventricular function and a limited number of coexisting conditions. Very fewer number of triple vessel disease were taken in to consideration. The majority of patients who undergo bypass surgery have three-vessel disease; less than one percent has single-vessel disease. This was the case in 23 percent and 26 percent of the study patients, respectively. In current practice, however, off-pump surgery is increasingly being performed in patients with single- and double-vessel disease, (Hernandez et al., 2001).

Hence high risk patients were not taken in to consideration in the study. There were 281 patients who were enrolled in the study, but out of which only 70 patients underwent angiography, rest declined to the above cause. This can definitely cause a bias in the study and give misleading results. It may affect the overall outcome of the graft patency in each of the groups and to find out which procedure is more effective can be difficult to pull up. As mentioned before that on-pump is more performed on triple vessel disease rather single or double, vice versa for off-pump procedure. It may have a different set of results which can develop due to this.

Overall the study done has shown no difference in outcomes of the procedures. If the bias for choosing the patients been removed it would give excellent results for the same.

Lingaas et al., (2004)

Clinical and Angiographic Outcome of Coronary Surgery with and without Cardiopulmonary Bypass: A Prospective Randomized Trial

Aim: The aim of this randomized study was to compare perioperative morbidity and mortality and intraoperative and short term graft patency in off-pump and on-pump CABG.

Methods: Patients with stable angina pectoris and moderate or good left ventricular function eligible for coronary artery bypass surgery were included if off-pump surgery was considered possible. One hundred twenty patients were included between March 1999 and March 2002. The patients were randomized in blocks of twenty. This system allowed minor changes in protocol during the study without bias of randomization.

In the first forty cases, patients with significant lesions of the circumflex artery were excluded from the study, because the table of the angiography system (Advantix; GE Medical Systems, Milwaukee, WI, USA) could not be tilted sideways to facilitate surgery on the posterior wall. In the last Eighty cases, the operation was performed on a tiltable angiography table (Koordinat OR; Siemens, Erlangen, Germany) combined with Angiostar Plus operating room angiographic equipment (Siemens), and the anatomical location of stenosis was no longer an exclusion criteria

Results: Coronary angiography of the bypass grafts was performed intra-operatively and at three months and the follow-up was done by two experienced interventional radiologists blinded to the operative technique. The angiography at follow-up also included visualizations of the native coronary vessels. Patency was defined as any flow through the graft or the native vessel (FitzGibbon class A and B), (FitzGibbon, Burton & Leach, 1978). Patients with significant and clinically important stenosis or occlusions at follow-up were admitted to percutaneous coronary intervention (PCI) if indicated.

Of the 120 patients, 117 were examined at three months; two had died and one was lost to follow-up. Of the patients examined, 115 underwent both coronary and graft angiography at follow-up. The total graft patency was 89% and 94% in off-pump and on-pump respectively. The P value was not significant. Risk difference at 95% Confidence interval 5 (- 2.6 to 12.6).

Author's Conclusion: They concluded that in this prospective, controlled study, peri-operative and short-term outcome of off-pump coronary surgery equaled that of on-pump surgery. Hence no difference in the outcomes was noticed at the end of 3 months in the overall graft patency.

Reviewer's opinion & Limitations:

There was no significant difference in the overall graft patency in both the groups. Hence off pump can be performed with the same intermediate graft patency as on-pump surgery.

However if we look at it closely there has been more graft revision in the off-pump group during the surgery after intraoperative angiographic control. This shows that off pump is technically more demanding. Therefore if Intraoperative angiography was not performed then the overall result would be definitely different at the end of three months. However, it is likely that most of the grafts revised because of angiographic findings of surgery related failure or poor runoff would have occluded before the end of the three-month follow-up period. The revision of graft was done due to anastomotic technical failure and after their revision the patency was equal in both groups at the end of 3 months.

This study was good but few changes were made intraoperatively, so this might affected the result overall because revision of graft intra-operatively can give false result of the actual procedure. Further they did a prospective study and hence 12 months follow-up was done later. This is discussed in the next paper.

Lingaas et al., (2006)

Clinical and Radiologic Outcome of Off-Pump Coronary Surgery at 12 Months Follow-Up: A Prospective Randomized Trial

Aim: The aim of this study was to compare off-pump and on-pump surgery on the appearance of graft patency, myocardial function, and clinical outcome after twelve months.

Methods: Patients with stable angina pectoris and moderate or good left ventricular function eligible for coronary artery bypass surgery were included if off-pump surgery was considered possible. One hundred twenty patients were included between March 1999 and March 2002. The patients were randomized in blocks of twenty. This system allowed minor changes in protocol during the study without bias of randomization.

In the first forty cases, patients with significant lesions of the circumflex artery were excluded from the study, because the table of the angiography system (Advantix; GE Medical Systems, Milwaukee, WI, USA) could not be tilted sideways to facilitate surgery on the posterior wall. In the last eighty cases, the operation was performed on a tiltable angiography table (Koordinat OR; Siemens, Erlangen, Germany) combined with Angiostar Plus operating room angiographic equipment (Siemens), and the anatomical location of stenosis was no longer an exclusion criteria

Results: Coronary angiography of the bypass grafts was performed intra-operatively and at three months and then at twelve months, the follow-up was done by two experienced interventional radiologists blinded to the operative technique. The angiography at follow-up also included visualizations of the native coronary vessels. Patency was defined as any flow through the graft or the native vessel (FitzGibbon class A and B), (FitzGibbon, Burton & Leach, 1978). Patients with significant and clinically important stenosis or occlusions at follow-up were admitted to percutaneous coronary intervention (PCI) if indicated

At twelve months, 112 of 120 patients were readmitted for follow-up study, and angiography was performed in 109 patients. The total graft patency was 85% and 90% in off-pump and on-pump respectively. The P value was not significant. Risk difference at 95% Confidence Interval, 5 (- 2.6 to 12.6).

Author's Conclusion: He reported that the randomized study did not reveal any significant differences between off-pump and on-pump coronary bypass surgery with regard to clinical and angiographic endpoints 12 months after operation.

Reviewer's opinion & Limitations:

There was no significant difference in the overall graft patency in both the groups. Hence off pump can be performed with the same intermediate graft patency as on-pump surgery.

Only 120 patients included gave a relatively low statistical power, but the emphasis has been on the quality of the data with a complex and resource demanding follow-up. Due to the varying degrees of initial training by the

surgeons involved, they had a learning curve, reflected in the relatively high number of conversions. This may not be completely representative for the current state of the art in off-pump surgery, although all centers have surgeons with varying experience. The design of the study with intraoperative and postoperative routine angiography led to additional interventions (revision of the grafts and percutaneous interventions) that altered the outcome. Many of these corrections may have been unnecessary. However, it is difficult to predict the effect on the outcome if these had not been done, hence the actual result would have been different.

Puskas et al., (2004)

Off-Pump vs. Conventional Coronary Artery Bypass Grafting: Early and 1-Year Graft Patency, Cost, and Quality-of-Life Outcomes

Aim: To assess graft patency, clinical and quality-of-life outcomes, and cost among patients while in the hospital and at 1-year follow-up.

Methods: Flowchart below depicts the methods in which the patients were included in the study. All surgeries were performed by a single experienced surgeon and all patient management was conducted by a single team. Patients, their families, referring cardiologists, and non-operative clinicians were blinded to treatment strategy for one year. Randomization occurred after documentation by the surgeon of the intended optimal revascularization. Patients were randomly assigned by means of a computer-generated random number table and were stratified by sex and diabetic status. Random assignment was performed separately within each stratum with randomly permuted block sizes of four and six. Three patients (One in the CABG with cardiopulmonary bypass group and two in the OPCAB group) were found after randomization to require mitral valve repair or replacement and were withdrawn. Therefore, the study population included 197 patients.

Patient management was governed by unbiased and criteria-driven printed protocols that were applied similarly to both groups.

Flowchart 1: Methods of Surgical Management of Arterial Revascularization Therapies (SMART) Trial, (Puskas et al., 2004)

Results: Of the 189 patients who were alive at one year, 153 (81%) had coronary angiography done. Overall, 93.6% of grafts were patent among OPCAB patients compared with 95.8% of the grafts among CABG with cardiopulmonary bypass patients, with a P value of 0.27 which is not significant. Risk difference at 95% Confidence interval was 2.1 (- 1.7 to 6.0). Hence patency was similar between groups at one year among all arterial conduits, all venous conduits, and among grafts to each region of the heart.

Author's Conclusion: The author concluded that in this randomized single-surgeon trial among unselected patients with angiographic follow-up; OPCAB achieved similar graft patency in the hospital and at 1 year. OPCAB may provide complete revascularization that is durable and cost-effective.

Reviewer's opinion & Limitations:

The study showed that there is no significant difference in the graft patency. Hence both procedures are capable in attaining effective patency and the end of one year. But there are certain limitations in this study which will help us know a bit more about it. The performance of both the procedures' was done by a single surgeon, which reduces the surgical variability, thus making the groups more comparable; but the generalizability of the findings to other surgeons and health care systems cannot be demonstrated. Another important

limitation is that one-year follow-up angiography was only obtained in 78% of the enrolled patients (81% of one-year survivors). Although there was no systematic difference between the 2 groups regarding lack of one-year angiography, hence they cannot exclude the possibility of selection biases affecting their findings. This type of limitation is inherent in trials that require patients to undergo invasive follow-up procedures.

Hence the results from the SMART trial demonstrate that OPCAB may provide complete revascularization that is durable relative to CABG with cardiopulmonary bypass when performed on unselected patients undergoing elective, isolated CABG. A larger multicenter trial of OPCAB compared with CABG with cardiopulmonary bypass is needed to evaluate the generalizability of these results and to better clarify the role of OPCAB in the routine care of patients with multivessel coronary artery disease.

Kobayashi et al, (2005)

Early Outcome of a Randomized Comparison of Off-Pump and On-Pump Multiple Arterial Coronary Revascularization

Aim: The aim was to perform a prospective randomized controlled study to compare off-pump and on-pump CABG with multiple arterial grafts.

Methods: Between July, 2002, and September, 2004, 167 consecutive unselected patients referred for elective primary CABG were randomly assigned to undergo multiple arterial off-pump CABG (n=81) or on-pump CABG (n=86). Early graft patency was examined within three weeks after the operation by coronary angiography. This study was known as The Japanese Off-pump Coronary Revascularization Investigation (JOCRI), and was designed to compare the early outcome of off-pump and on-pump coronary revascularization in patients with a low risk for CPB over a Three-year period. The primary end points were Three-year cardiac events after CABG, including acute myocardial infarction, admission for angina pectoris or congestive heart failure, cardiac death, and re-intervention. The secondary end points were completeness of revascularization, early clinical outcomes, and neurocognitive function. This was a prospective, randomized, controlled multicenter trial performed in five centers, with single surgeon in each center.

Results: All patients underwent postoperative angiography to evaluate the graft patency within three weeks after CABG. The interventional cardiologists were

blinded to group assignment for angiographic evaluation. The graft patency was defined when the anastomosed site and graft were opacified by contrast medium either via the conduit or native coronary artery. Flow competition or string sign was not defined as occlusion. The quality of the grafts was assessed using the criteria of, (FitzGibbon et al, 1986).

All the patients enrolled in the study went for angiographic follow up. The total graft patency was 94% and 96% in the OPCAB and CABG with CPB groups respectively, with a P value of 0.093 which is not significant. The Risk difference was not recorded in this paper.

Author's Conclusion: They concluded that off-pump CABG with multiple arterial grafts was as safe as the conventional on-pump CABG, with similar completeness of revascularization and early graft patency.

Reviewer's opinion & Limitations:

According to this study there is no significant difference in the graft patency between the two procedures. But the angiography was taken within three weeks which actually is too early to interpret the results of a study.

This study was undertaken after the operating surgeons in each hospital had performed more than 200 OPCAB cases with multiple arterial grafts. Thus, complete multiple arterial coronary revascularizations without CPB was possible in almost all cases. The graft patency was the same irrespective of CPB use. The stenosis-free graft patency rate, however, was slightly worse in the off-pump group, though the difference was not statistically significant. Hence there are a

few limitations in this study. The surgeons are very well trained in OPCAB so it does affect the study. A drawback of this study is that the study groups were composed of highly selected low-risk patients and not the general population at large. In addition, OPCAB was performed by experienced surgeons and the results may not be the same with surgeons in their learning curve period. These results might be true only for cardiac surgeons and anesthesiologists who are fully accustomed to OPCAB, rather than surgeons who are just learning the procedure. Also the data was collected by five centers where the procedures were performed; this might have some effect on the study as five different surgeons were performing with different surgical expertise.

Therefore effects of graft quality by OPCAB need to be examined by evaluation of long-term follow-up when compared with on-pump surgery. Also pooling of data should be done from a single centre rather pooling it from several centers.

Al-Ruzzeh et al., (2006)

Effect of off-pump coronary artery bypass surgery on clinical, angiographic, neurocognitive, and quality of life outcomes: randomized controlled trial.

Aim: The aim was to compare the clinical, angiographic, neurocognitive, and quality of life outcomes of off-pump coronary artery bypass surgery with conventional coronary artery bypass grafting surgery using cardiopulmonary bypass. But we only compared the angiographic outcomes.

Methods: The method of selection of patients is depicted in Flowchart below.

They prospectively randomized 168 patients to conventional coronary artery bypass grafting surgery using cardiopulmonary bypass (n = 84) or to off-pump coronary artery bypass grafting surgery. Blinding of the surgeon was not possible. All other staffs were blinded: medical, paramedical, and nursing staff on the intensive therapy unit, the ward staff, and the study staff, including the cardiologist who carried out the angiography and commented on the angiograms and the psychologist who carried out the tests for neurocognitive function. Patients and their relatives were also blinded to the procedure. Clinical decisions on patient management on the intensive therapy unit and the ward were taken by blinded staff and were based on local protocols and guidelines, including decisions on extubation, blood transfusion, and discharge. To ensure complete

blinding the type of procedure was not stated in the clinical notes or in any correspondence.

Flowchart 1: Methods of selection of patients, (Al-Ruzzeh, 2006).

Results: Overall 151 (90%) patients underwent angiography three months postoperatively: 75 in the off-pump group and 76 in the cardiopulmonary bypass group, providing 461 grafts for analysis. The total graft patency was 93% and 94% in OPCAB and CABG with CPB group respectively. The P value was not significant. The Risk difference at 95% Confidence interval was 1.4 (- 3.8 to 6.6).

Author's Conclusion: They concluded that Patients who underwent off-pump coronary artery bypass surgery showed similar patency of grafts; better clinical outcome than patients who underwent conventional coronary artery bypass grafting surgery using cardiopulmonary bypass.

Reviewer's opinion & Limitations:

The author has done a very good study. It interprets that there is no significant difference in the graft patency when compared by the two procedures

To minimize or eliminate bias from differences in learning curves, surgeons, centers, and conduits, they gained experience, before starting the trial, from non-selective use of the off-pump technique in more than 500 unselected patients, using different types of arterial and venous grafts. But they only followed up for three months, when a long term follow-up is required.

The Limitation of this study is that if a long term follow up is required then large sample size is essential in order to get efficient results. According to the author another limitation of the trial was that the power calculation was based on a relatively high expected patency rate (96%), which could have influenced the

sample size required for this trial aimed to test equivalence rather than superiority.

Hence a nice study in which the author has tried every minimum ways to eliminate the bias and tried to give a real picture of the results. There has been effort made to eliminate the bias in order to produce efficient and clear results.

Angelini et al., (2009)

Effects of on- and off-pump coronary artery surgery on graft patency, survival, and health-related quality of life: Long-term follow-up of 2 randomized controlled trials

Aim: The aim was to compare long-term graft patency in patients randomized to off-pump coronary artery bypass or coronary artery bypass grafting with cardiopulmonary bypass.

Methods: The study was done by pooling the data using two trials done by the authors, the trial is known as Beating Heart Against Cardioplegic Arrest Study 1&2 (BHACAS). Patients were recruited from March 1997 to August 1998 (BHACAS 1) and from September 1998 to November 1999 (BHACAS 2). Participants were randomly assigned to the OPCAB or CABG–CPB groups. The follow-up was done after 7 years and 199 patients were selected for Multidetector Computed Tomography Coronary Angiography (MDTCA). The flowchart below depicts the method of selection of the patients in both the trials and the distribution followed by the follow-up of the participants. Hence after seven years, out of 401 patients only 199 came for the follow-up.

Flowchart 1: Trial profiles for Beating Heart Against Cardioplegic Arrest Study 1&2 (Angelini et al., 2002).

Results: After pooling of data from BHACAS 1 and 2, the total graft patency was 89% and 89.4% in OPCAB and CABG with CPB respectively. The P value was >0.99 which is not significant. The Risk difference at 95% Confidence interval was 1 (0.55 to 1.81).

Author's Conclusion: They concluded that long-term health outcomes and graft patency with off-pump coronary artery bypass are similar to those with

coronary artery bypass grafting with cardiopulmonary bypass when both operations are performed by experienced surgeons.

Reviewer's opinion & Limitations:

The author has done a very good study which involves a long term follow-up in order to compare the long term patency of grafts. Hence the results obtained shows that there is no significant difference in the graft patency's when done with OPCAB or CABG with CPB.

Randomized allocation, which minimizes selection bias, is an important strength of the BHACAS trials. A further strength is the high proportion of screened patients who were recruited (almost 50%) enhancing the applicability of the findings in their center, (Angelini et al., 2002). Attrition during the 6 to 8 years of follow-up is the main limitation, of this trial. As initially 401 patients were randomized. Out of which only 199 went under MDTCA. The main reason was that the patients declined to be further investigated.

Finally, it is important to remember that the BHACAS trials were carried out in a single center by a single academic surgical team. This surgical team has documented innovations in OPCAB technique, their performance and that of residents learning OPCAB, and other aspects of their experience with OPCAB over more than a decade. Therefore a definite caution should be exercised in generalizing these findings to other surgeons and centers. The results won't be the same if performed by an inexperienced surgeon in some other center.

Discussion of the Key Papers:

The debate concerning the potential clinical advantages of the off-pump CABG versus on-pump CABG approach for surgical coronary revascularization is still open. Even if different approaches have been used to try to improve knowledge on this topic, e.g., retrospective and prospective analysis of several vast randomized patient series, the results emerging are difficult to interpret because of selection bias and other potential limitations of different studies. This systematic review of randomized studies has addressed the question of whether or not a more demanding surgical technique (OPCAB) can provide similar graft patency rates with respect to standard surgical therapy (CABG). As previously mentioned for hard outcomes assessment, the number of patients enrolled, as well as the number of anastomosis performed and subsequently restudied with angiography, did not reach any significance to detect possible differences in patency among the groups.

In this systematic review the study of (Czerny et al., 2001) and (Khan et al., 2004), there was a significant difference in the patency rates in both groups and on pump was superior to off pump. But when tried to scrutinize the paper it fell well below the criteria of Jadad scale and scored poor on it. The outcomes were compared for a short amount of time but due to this potential bias it could not be said a study of good results. Khan et al., 2004 had compared the above two procedures but eventually the pitfalls of the study was the learning curve for the surgeon. As the off-pump surgery requires more skill and expertise, the surgeons performing in this study were not so experienced in the performing the

off-pump surgery which eventually gave good results in favor of on-pump surgery. This was a definite limitation in the study.

As with all surgical trials, the results are influenced by the level of experience of the surgeon. Currently, the evidence generated from our review that off-pump surgery represents data acquired from only a handful of surgeons. It is difficult to determine how applicable the results are to a population of cardiac surgeons with different levels of experience and ability as it would definitely create a positive or a negative impact on the study.

We compared the outcomes on a short and long term basis, to enhance and find out if it gives any different results. But we found no difference in the patency rates when compared at 3 months, 1 year and also at 7 years. This doesn't means that there is no difference in the two procedures as every paper had it own limitation which includes selection of the patient, surgical skills, follow up time and losing the patients in long term follow-ups.

In our study, Nathoe et al., (2003) found no significance in the patency rates when both the procedures were compared. But to look in more depth they focused on a relatively low-risk population of patients. The mean age of the patients was 61 years, and the majority had single or double-vessel disease with preserved ventricular function and a limited number of coexisting conditions. Therefore no high risk patients were involved in their study. This may have an effect on the overall outcome because if high risk patients are included then it would definitely give a different outcome.

Lingaas et al., (2006) compared the patency rates at three months and one year, there was no significant difference in the patency rates between the two groups. The drawback of this study was again the learning curve due to the varying degrees of initial training by the surgeons involved which reflected in the relatively high number of conversions from off-pump to on-pump surgery. This shows off-pump surgery does require a lot of skill in order do expertise in it. This definitely affects the study and gives varying result.

Al-Ruzzeh et al., (2006) did a very good study. To minimize or eliminate bias from differences in learning curves, surgeons, centers, and conduits, they gained experience, before starting the trial, from non-selective use of the off-pump technique in more than 500 unselected patients, using different types of arterial and venous grafts. Hence by doing this they actually eliminate the bias of the learning curve, eventually they found no significant difference in the patency when compared with off-pump and on-pump surgery. Does this signify that learning curve has an effect on the overall result?? As our above two studies did have a learning curve but still they showed no significant difference in the patency rates. Hence this topic needs a further research in terms of surgeon's skills for the procedure to be opted.

Angelini et al., (2009) did a huge study with a follow up of seven years. The data was pooled from two trials which are known as Beating Heart Against Cardioplegic Arrest Study 1&2. There were in all 401 patients enrolled out of which only 199 underwent MDTCA, hence there was a definite drop in the patients follow-up due to seven years of gap. The main reason for the patients

not turning up because they don't wanted to be re-investigated. This study also showed no significance in the patency rates even after seven years. The surgeons in this study were relatively experienced in OPCAB; hence the probability of bias was removed, and also it was a single center trial. Therefore again and again the learning skill for OPCAB comes in to play. But eventually none of the studies show any significant difference irrespective of the learning curve of the procedure. This interprets that both the procedures are equally effective in their own way, but still research needs to be done in order to know if a learning curve affects the study or not.

In Lingaas et al., 2004 study the surgeons did an intra-operative coronary angiography which helped them know that there was some blockage which was corrected intra-operatively. This does help them give a different result post-operatively. Because if they wouldn't have done the correction then it would have given a negative result which means the patency rates would be significant in both procedures.

All the review papers included in the study are on a low to medium risk patients; the high risk patients are eliminated. Also no emergency procedures were included in the study; this may be a definite limitation of the systematic review. The review compared the outcomes on a short term and long term basis. Hence the results are then compared as an overall rather committing to a fixed period of time. In this review we did not compare the arterial and venous graft patency individually. It would be really difficult to compare arterial grafts for on-pump and off-pump individually and same for the venous graft. Hence in this

study there was comparison of the total patency rate which included arterial and venous grafts each and then compared with the two procedures. By this it gave us a clear overview of the results between the two procedures. There was no significant difference when the patency rates were compared between on-pump CABG and off-pump CABG. But there was some difference in the patency rate when compared with arterial and venous grafts.

Venous grafts were more patent in the on-pump group whilst the arterial grafts were more patent in the off- pump group, does this signifies that more venous grafts to be used when performing on-pump CABG and vice versa for arterial grafts? This need to be studied in detail and it is the area for further research. But eventually when on a whole patency is compared there is no significant difference statistically.

Hence our main aim for doing this study was to evaluate the efficacy in terms of patency when compared on a short and long term outcomes. The limitations were present in each study, but every minute way to eliminate the bias was taken in to consideration. But still there is a large area of research to be done in order to authenticate and acknowledge a given procedure in order to consider in effective and efficient.

REVIEWERS CONCLUSION:

After reviewing these papers we come to a conclusion that OPCAB and CABG with CPB when compared in terms of patency rates, gives the same results. We couldn't find any significant difference in the patency rates when compared with the two procedures.

With increasing experience, OPCAB can be safely performed in un-selected patients. In fact, more than patient condition, an individual surgeon's competence and common sense are probably the most important selection criteria for OPCAB surgery. Hence, the argument that only a select few can benefit from OPCAB no longer holds true. In the last decade or so, OPCAB has been tested through an increasingly rigorous process of scientific validation. From a large number of observational, case-matched, retrospective analyses to randomized controlled trials, there is plenty of evidence that OPCAB surgery is now a proven effective when compared to CABG with CPB.

I had emailed some authors who are eminent Cardiac Surgeons and who have performed many cardiac surgeries including OPCAB and CABG. My question to them was that why they are trying to demolish CABG with CPB over OPCAB, when both give efficient results. One of author quoted me his answer "**I fully agree with your view that on-pump has its place and that there are certain subgroups of patients where on-pump may have an edge over off-pump. In fact in situations like emergency CABG for acute myocardial infarction occasionally surgery is performed on-pump with beating heart using off-pump stabilizer to achieve maximum benefit. Similarly when combined**

procedures such as aortic valve replacement and CABG are to be done, then on-pump is the technique of choice. **What you find in literature is a comparison of the two techniques and the available evidence seems to suggest that either one can be used with good results. There are some contraindications for both techniques and I'm sure you are aware of them"**

Hence it actually shows their view that both the procedures are helpful to the patients depending on the clinical condition of the particular patient rather blaming a procedure for not giving efficient results.

But again there must be more research to be done in patients who are high risk rather doing a study in a low risk group of patients, on a long term and with more diseased vessel rather involving single or double vessel, and hence their results when compared would give better view of the actual scenario.

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Area for further research:

The need for further research in this topic is definitely required in order to implement the results to a wide range of population suffering from cardiovascular disease and hence undergoing cardiac surgeries

Randomized trial should be done more in order to get efficient results and avoidance of any bias in the study. Selection criteria should be broadened. Instead of usual selection of low risk patients, trials should be conducted on high risk patients. Triple vessel disease should be include more as it gives the chance to interpret much better outcomes of a procedure, rather taking single or double vessel disease.

The trials should not be done if the surgeons are in the learning curve period of a procedure as this gives a different set of results when compared with surgeons who have expertise in the same procedure. The follow-up is the most important criteria in order to interpret the efficacy of the procedure, hence long term follow-up should be taken in to consideration rather a mere short term.

Large multicenter trials are required in order to compare the two procedures and get the best result out of it and hence establish a new advance technique to promote better outcomes in terms of patency.

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Appendix 1

The Jadad Scale (1996)

Instrument to Measure the Likelihood of Bias in Pain Research Reports This is not the same as being asked to review a paper. It should not take more than 10 minutes to score a report and there is no right or wrong answers. Please read the article and try to answer the following questions.

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?

2. Was the study described as double blind?

3. Was there a description of withdrawals and dropouts?

Blind Assessment of the Quality of Trial Reports

Scoring the items:

Either give a score of 1 point for each ”yes” or 0 points for each “no.” There are no in-between marks.

Give 1 additional point if: For question 1, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)

and/or: If for question 2 the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)

Deduct 1 point if: For question 1, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)

and/or: For question 2, the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy)

Guidelines for Assessment

1. Randomization

A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should be not regarded as appropriate.

2. Single/Double blinding

A study must be regarded as double blind if the word “double blind” is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.

3. Withdrawals and dropouts

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

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APPENDIX 2:

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)
(For definitions of terms used see glossary at http://www.cebm.net/?o=1116)

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